Peer Review File

Reviewer Comments
The study presented is meaningful as it has the potential to improve stroke screening to aid in clinical decision making. However, some revisions are suggested:

Reply：

Thank you for the reviewers' kindly and earnestly review! Your questions and suggestions help us take a new look at this study and enlighten us on further study.

Introduction:
-The authors mention it is not clear if DNT would be influenced by SSS, but it seems fairly obvious it would be since time needs to be taken to answer the SSS questionnaire. Even if the questionnaire can be answered, form prior medical history, no all patients will have past documentation.

Reply 1:
Thank you for your kindly reminder. Our introduction of the SSS project was insufficient and clear. SSS (stroke screening survey) refers to the "community stroke screening". In the (selected) community, all populations, above a certain age were invited to voluntarily finish the questionnaire to assess their stroke risk(DeLemos, Atkinson et al. 2003). It is a kind of stroke prevention project conducted in many countries since decades ago (Bharucha, Bharucha et al. 1988).

In China, the National SSS was established by the Chinese Ministry of Health in 2013 to prevent and manage stroke. The screening program was implemented in two stages. In the first stage, using a 2-stage stratified cluster sampling method, communities were selected in proportion to the local population size. The cluster sampling method was used in every primary sampling unit, and all residents aged 40 years or older in the selected communities were invited to participate in the first stage of the screening program, which was conducted in nearby community hospitals or health stations. The participants were invited via telephone. Trained researchers interviewed participants face to face regarding stroke history and risk factors as well as demographic information (age, gender, education level, etc.). In the second stage, participants who had a history of stroke were interviewed again for additional details about their stroke histories and risk factors, including information on smoking, alcohol consumption, physical activity, hypertension, diabetes. Physical and laboratory examinations (serum lipids and glucose) were also performed.

As for Jiading district, the whole population SSS formally started since 2017, the residents in Jiading district aged 35 and over were invited to participate in the survey voluntarily. That is to say the SSS object is the whole residences in each community instead of the stroke patients in hospital. The DNT denotes the time between hospital arrival and administration of intravenous thrombolysis (Van Schaik, Van der Veen et al. 2014). Thus, for the patients who participated the SSS, they did not answer the questionnaire after stroke onset and in hospital. The DNT time did not include the answering time and won't be affected by the answering time. More clues can be found on page 8, line 156-161.

Changes in the text:

See page 5, line 99-102; page 6, line 108-110; page 7, line 145.

We have modified the text as "Stroke screening survey (SSS), **a community-based stroke surveillance program among residents**, which uses a structured face-to-face questionnaire to obtain information about the presence of risk factors and stroke history, was established in 2013 in China to promote the prevention of stroke."

"(termed the "door-to-needle time", DNT, **which means the time between hospital arrival and administration of intravenous thrombolysis**)"

"From 2017, Jiading District, Shanghai, carried out the SSS program, which was free to screen the stroke risk factors for **community** residents, aged 35 and over, voluntarily in Jiading to identify the high-risk group for stroke."

-It would be helpful to include exactly what questions are on the SSS questionnaire to aid the reader in correlating how beneficial they may be to the study.

Reply2:

Thank you for your splendid advice. We have attached the original Chinese version "Risk Assessment Form for High-Risk Stroke Population Screening and Intervention Projects in 2013" and its English translation version as the supplementary materials as you suggested. This form is a national SSS assessment questionnaire, established by the group of "National Health and Family Planning Commission's "12th Five Year Plan" Health Care Reform Project -- Screening and Intervention Project for High-Risk Groups of Stroke" in 2012. The detailed information of this project can be found on the official website (http://www.sinosc.org/NewsInfo/SCPH/SCPHIndex?cCode=0003).

The only difference in the screening questionnaire between Jiading District, Shanghai, and the national version is the youngest age for interviewees. In the national version, the youngest interview was 40 years old. And the Jiading district lowered the age threshold to 35 years old, as we mentioned in the manuscript (page 7, line 145)

Changes in the text:

See the change in the separate supplementary file and the two Appendix files (Appendix

1. Risk Assessment Form for High-Risk Stroke Population Screening and Intervention Projects in 2013 (original-CHINESE).docx; Appendix 2. Risk Assessment Form for High-Risk Stroke Population Screening and Intervention Projects in 2013 (translation-ENGLISH).docx).

Methods:

-Death was considered a failure for this study, but was it considered to look into poor clinical outcomes as well? Potentially, looking into more subgroups of outcomes that could occur.

Reply3:

Thank you for your important question and great advice. During conducting this study, we were curious about how the SSS affects stroke patients' health condition with time going, like in each stage since the onset. However, the indicators of the clinical outcomes (got from SSSS database), like the NIHSS score on discharge (49.27% missing value), the mRS (Modified Rankin Score) on discharge (49.35% missing value), the adverse reaction in hospital (all less than 2% happened), et al., contained too much missing data or less variation. It led to the invalid conclusion based on those indicators, to say nothing of subgroup analysis. The same limitations happened to the survival analysis. 30 patients died in hospital (all non-previous patients); 50 patients (8 previous SSS and 42 non-previous SSS) died within 30 days after discharge, and 81 patients (12 screened and 69 non-screened) died in 90 days after discharge. However, there were 8 patients leaving hospital less than 30 days and 32 patients leaving hospital less than 90 days. Thus, 30-day and 90-day mortality after discharge could not be used in this study yet.

Therefore, the survival analysis was applied to fit for this right censoring living data, to make full use of the data information and get relatively reliable conclusion (Mittelman, Ferris et al. 1996, Geng, Emenyonu et al. 2008, Rosen, Prasad et al. 2020). We hope that the findings we presented based on the limited data could provide a clue for peer scholars to pay more attention to the effect of SSS on stroke patients instead of just on the morbidity of healthy people. Actually, we are trying to collect more recent and comprehensive data, including some questionnaire data, to investigate the effect of SSS on more outcomes and its mechanism.

Thus, limited to the quality of the real-world data involved, we could not conduct more empirical analysis with more clinical outcomes in this study. We have added this point into the limitation in the text.

Changes in the text:

See page 15, line 339-343.

We have added: "Thirdly, due to the quality of the real-world data involved, too much missing data, and relatively less variation, we could not conduct more empirical

analysis with more clinical outcomes in this study. However, we are planning to implement this in the future by collecting more and high-quality data."

Results and Discussion:

-It is stated patients with SSS before onset were older, but how much older? Was it to a significant degree? Was this part of the reason they were screened in such a manner? If so, would that not make the study bias as only older patients are screened this way?

Reply4:

Thank you for your important questions. Our careless omission only showed the baseline difference between the previous SSS and non-previous SSS groups but not described it in the text clearly. We have modified the text to be more explicit.

Firstly, as shown in Table 1, the median age of patients in the previous SSS group (75, IQR 70-83) was 2 two years older than patients in the non-previous SSS groups (73, IQR 65-82). This difference was significant due to the P-value (0,017) of the Mann-Whitney test.

Secondly, we agreed with your assumption about the resource of the age difference. In the "DISCUSSION" part (page 11-12; line 249-255), we attributed the age bias to the SSS manner in Jiading. Because GPs carried out the SSS in Jiading in the community health service centers. Those GPs were likely to pay more attention to residences that they are more familiar with and with more risk factors. Those residences were more likely to be older and with more diseases, which resulted in the bias of age, prevalence of hypertension, and diabetes.

Thirdly, to adjust the significant bias, including the onset age (P=0.017), the prevalence of hypertension (P=0.02) and diabetes (P<0.001), and even overweight (P=0.091) (Table 1, left part), between the previous SSS group and non-previous SSS group, Propensity Score Matching (PSM) analysis was used. After matching, the demographic characteristics of the two groups were balanced. As shown in table 1 right 3 columns, there was no significant demographic characteristics difference between the two matching groups (all P>0.1). Therefore, the conclusion based on the matching groups won't be affected by the bias of the original screening manner.

Changes in the text:

See page 10, line 212-221.

We have modified the text as: "The median onset age of these patients was 75 years (IQR [70-83]), and 417 (37.50%) were female. Furthermore, 241(23.30%) patients died for all-cause by January 8, 2020, including 30 patients who died in stroke centers. Patients with SSS before AIS onset were significantly older than patients without SSS before AIS (73 [65-82]; P<0.05), with a much higher percentage of the history of hypertension (90.23% VS 78.51%) and history of diabetes mellitus (50.00% VS 25.81%). (Table 1). Thus, we should take those indicators under control to explore the

stroke screening effect on stroke treatment. After adjusting the bias of demographic characteristics by PSM, those demographic characteristics in the previous SSS group and non-previous SSS group were balanced (P>0.1, Table 1)."

-Another limitation to the manuscript that should be added is the relatively low NIHSS score seen for these patients. A score of 3 indicates many of the patients did not have severe strokes and a follow-up may be beneficial to so how this screening system would aid in decision making for severe large vessel occlusion patients.

Reply5:

Thank you for your kindly reminder. We have noted the feature of those stroke patients. But sorry for the ambiguous text in the "STRENGTH AND LIMITATIONS". We have modified the text to be clearer.

As for the value of this study to the severe large vessel occlusion patients, as we had shown in the text, the SSS was significantly associate with shorter DNT (30 [24,49] VS 44[31.5,49]). Many studies have justified that Earlier intravenous thrombolysis administration is also associated with lower risks for complications, including symptomatic intracranial hemorrhage (Fonarow, Zhao et al. 2014) . However, compared to severe stroke, minor stroke patients are less likely to benefit from intravenous thrombolysis, and fewer of them were treated by intravenous thrombolysis (Wang, Wang et al. 2013, Berge, Whiteley et al. 2021). That may indicate the severe stroke patients can get more benefit from the screening. Nevertheless, this hypothesis remains to be further confirmed.

Changes in the text:

See page 15, line 343-346.

We have modified the text as: "Fourthly, limited to the minor stroke onset situation of the sample in this study, the effect of SSS on those minor stroke patients was less reliable to the extent to severer stroke patients (NIHSS>3). Further studies should be done to extend those findings in this study."

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